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(19)

(54) A SALT OF A GUANIDINE DERIVATIVE

(71) We, RECKITT & COLMAN PRODUCTS LIMITED, a British Company, of P.O. Box 26, 1/17 Burlington Lane, London, W.4., do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel compound, to processes for its preparation and to its use as a biocide.

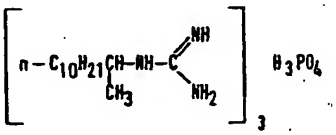
Untold damage is caused by unwanted degradation and deterioration of materials by a wide range of fungal species. Wood, paper and cellulose fabrics are particularly prone to attack under damp or moist conditions while a wide variety of other materials such as wall-paper paste, aviation fuel and cutting oils may serve as substrates for deteriogens. Living plants and seeds of economic importance are also frequently savaged by fungal attack. Algae are less destructive in their habits than fungi but the presence of enormous growths of algae in inland waters, reservoirs, swimming pools, and water-cooling systems causes many problems for man, while the wide spread growth of algae on surfaces of the exteriors of buildings, particularly prevalent under tropical conditions, causes much disfigurement.

Biocides for the control of deleterious fungi and algae are well-known and widely used. However, the most useful biocides such as aryl mercury compounds and penta-chlorophenol are also highly toxic to plants and animals, including man. Further, most of these biocides are not readily biodegradable and their widespread use leads to environmental problems.

In recent years attention has been turned to a variety of organic fungicides and algicides. These may be used often as water-soluble forms, or as insoluble derivatives. Frequently water-insoluble derivatives have only a very low fungicidal action while water-soluble forms are often readily washed away or leached from the substrate by the water which of necessity is present when fungi and algae flourish.

We have now found that algae and fungi of a wide range of species are killed or controlled by the use of small amounts of a novel salt of a guanidine derivative.

According to this invention there is provided 2-guanidino dodecane phosphate of formula:—



The compound may be prepared by reacting 2-aminododecane with cyanamide in phosphoric acid. Alternatively, the corresponding acetate salt formed, for example, by reacting 2-aminododecane with cyanamide in acetic acid may be treated with aqueous trisodium phosphate to give the phosphate salt.

The compound has a very low mammalian toxicity (oral LD_{50} in mice 1g/kg), is not irritant, and yet has a very wide spectrum of activity against bacteria, fungi, algae and lichens. The solubility in water of the compound is 0.6 mg/ml at 20°C. This figure is low enough to ensure that the extent of leaching of the biocide from a treated substrate by water is very limited. On the other hand the water-solubility is

sufficiently high to give a concentration of material in a surrounding water-film which will control deteriogens.

The activity of 2-guanidino dodecane phosphate against bacteria is identical within experimental error, to that of a water-soluble salt, such as the hydrochloride or acetate. Surprisingly and unaccountably, the phosphate shows a perceptibly higher activity against a wide range of fungal species than does the acetate, while the phytotoxicity is unaccountably lower.

In the following plate spore germination tests performed according to the American Phytopathological Society's Committee on the standardisation of Fungicidal Tests the activity of 2-guanidino dodecane phosphate (GDP) was compared with that of 2-guanidino dodecane acetate (GDA) and n-dodecyl guanidine acetate (dodine) against a series of plant fungi.

Fungus	Fungicide	% inhibition of germination p.p.m. fungicide	
		1	10
Alternaria brassisicola	GDP	21	100
	GDP	41	100
	Dodine	31	100
Cephalosporium sp	GDA	29	100
	GDP	29	100
	Dodine	10	97
Fusarium culmorum	GDA	12	53
	GDP	9	100
	Dodine	4	55
Fusarium oxysporum	GDA	2	95
	GDP	10	100
	Dodine	6	100
Penicillium expansum	GDA	2	97
	GDP	30	100
	Dodine	6	100
Peziza ostracoderma	GDA	16	100
	GDP	26	100
	Dodine	3	100
Sclerotinia fructigena	GDA	3	68
	GDP	34	97
	Dodine	1	29

It will be seen that the phosphate salt has outstanding activity against all species, giving virtually 100% inhibition at a level of 10 p.p.m. even against resistant species such as sclerotina (cause of the economically important apple brown rot).

In further mycilial growth tests 2-guanidino dodecane phosphate was compared with the acetate and with dodine. The fungicide was incorporated into agar to give final concentrations of 100, 50, 10 and 1 p.p.m. Fungal mycelium was introduced onto the surface of the agar and the diameter of the growth obtained was measured in mm. after 7 days incubation.

Fungal	Fungicide	Diameter in mm Fungicide concentration				
		0	1	10	50	100ppm
Ascochyta pisi	GDA	42	49	20	15	14
	GDP	42	39	24	0	0
	Dodine	42	30	24	16	16
Cephalosporium sp.	GDA	68	68	68	51	39
	GDP	74	72	66	41	23
	Dodine	68	72	68	53	29
Fusarium culmorum	GDA	76	60	40	36	26
	GDP	85	62	43	36	18
	Dodine	76	63	46	41	24
Peziza ostracoderma	GDA	42	39	21	10	0
	GDP	42	30	12	0	0
	Dodine	42	38	25	19	14

The invention also provides a biocidal composition comprising as the active ingredient 2-guanidino dodecane phosphate in admixture with at least one diluent or carrier. The compositions may be in the form of solutions, emulsions, suspensions, powders, and granules. The compositions may also include non-ionic wetting and/or dispersing agents such as condensation products of an alkylene oxide with an organic alcohol or phenol.

As solid diluents or carriers there may be used inert absorbent carriers such as silicaceous earth. Suitable liquid diluents or carriers are aromatic hydrocarbons, e.g., xylene, mineral oil or alcohols such as 95% ethanol/5% water.

Compositions when formulated as liquids may contain from 0.05 to 5% by weight preferably 0.5 to 2% of 2-guanidino dodecane phosphate.

For the purposes of killing and inhibiting the fungal growth and germination of spores such as Aspergillus niger, Penicillium notatum, Trichophyton mentagrophytes and Epidermophyton floccusum which may occur in households on wallpaper, leather textiles, carpets and bathroom floor coverings, 2-guanidino dodecane phosphate may be applied as a liquid formulation using for example a sponge, or more conveniently as a self-propellant composition. A self-propellant composition may comprise 0.05 to 5% by weight, preferably 0.5 to 2%, 2-guanidino dodecane phosphate, 95 to 55% of a solvent such as a lower alcohol or glycol and 5 to 40% of a halocarbon or hydrocarbon propellant such as Arcton 12.

The following are examples of formulations containing 2-guanidino dodecane phosphate suitable for domestic purposes, for example cleansing walls and floors.

Liquid Formulation	
GDP	1.0 g
sodium tripolyphosphate	5.0 g
tetrasodium pyrophosphate	7.5 g
Ethylan CD 919	3.0 g
isopropanol	2.0 g
urea	4.0 g
water	77.5 g

In use tests showed that the composition afforded greater residual antifungal activity when compared with a similar composition in which the GDP had been replaced by a mixture of o-phenyl-phenol and a quaternary ammonium compound. (Ethylan is a Registered Trade Mark).

Self-propellant Composition

The following composition was filled into an 8 oz. aerosol container:

GDP	1.0 g
perfume	1.0 g
ethanol	151.85 g
Bitrex soln. (0.256% w/w)	0.15 g
Arcton 12	46.00 g

The composition when sprayed onto a surface afforded greater residual antifungal activity when compared with a similar composition from which the GDP had been omitted. (BITREX and ARCTON are Registered Trade Marks).

The invention also provides a method of combatting fungal growth which comprises applying to the fungus or to a fungal habitat 2-guanidino dodecane phosphate alone or in admixture with a dilent or carrier. In the method 2-guanidino dodecane phosphate suitably formulated may be applied directly to the fungus or fungal habitat or for some purposes it may be more convenient to apply a solution of a soluble salt (e.g. aqueous solution of the acetate) and then add an aqueous solution of trisodium phosphate so generating the phosphate salt *in situ*.

The preparation of 2-guanidino dodecane phosphate is illustrated in the following Examples. Unless otherwise stated, the ratios and percentages in the Examples are expressed in terms of weight/volume.

Example 1.

A mixture of 2-aminododecane (21.8g) and acetic acid (6g) was stirred at 98—100°C while cyanamide (8.9g) was added portionwise over two hours. The resultant mixture was stirred for a further three hours at 100°C, and after cooling acetic acid (0.6g) was added. On trituration with acetone the waxy mixture deposited crystals which were filtered off and recrystallised from acetone/isopropanol (1:1) to give 2-guanidinododecane acetate (18.5g) as colourless crystals, m.p. 150°C. (Found: C,63.0; H,11.6; N,14.6; $C_{15}H_{33}O_2N_3$ requires C,62.7; H,11.6; N,14.6%)

The product (shown by thin-layer chromatography to contain only one component) was dissolved in the minimum of hot water and a solution of trisodium phosphate (Na_3PO_4,8g) in water was added. The resultant gelatinous precipitate which was filtered off crystallised on drying at 100°C/50 mm (yield 16g).

Example 2.

Commercial grade 2-aminododecane (Armeen L 11 — Armour & Co., 1506g) was stirred with phosphoric acid (88%, 399g.) under reduced pressure (100 mm) at about 100°C whilst and aqueous solution of cyanamide (50%, 1230g) was added slowly, with stirring. Water was allowed to distil from the reaction mixture. After the addition (2 hours) the mixture was heated at 120°—130°C for 3 hours, then cooled to 80°C and washed several times with hot water, to remove dicyandiamide. The residual oil was dehydrated under reduced pressure giving a viscous gum consisting mainly of 2-guanidino dodecane phosphate. (ARMEEN is a Registered Trade Mark).

The *in vivo* fungicidal activity of 2-guanidino dodecane phosphate (GDP) is illustrated by the following Examples.

Example A.

Test panels of a garden fence coated with a heavy growth of green algae and lichens were painted with a 1% solution of GDP in isopropyl alcohol. Controls were painted with isopropyl alcohol only. After one week all organisms appeared dead. After three months the treated panels were free from algae and lichens but the controls were heavily coated with new growths.

Example B.

A rough-cast concrete wall facing west and covered with a variety of fungal growths was cleared by wire brushing with a weak solution of sodium hypochlorite. Part of the treated wall was sprayed with

an aqueous solution containing 0.1% GDP. After six months the control section of wall was heavily reinfested by fungi but the section treated with GDP was substantially free from fungal growths.

Example C.

The effect on the preservation of a cotton textile treated with 2-guanidino dodecane phosphate was compared with a control treated with distilled water only and also with cotton textiles treated with the acetate, with dodine or with laurylpentachlorophenate.

Standard test strips of cotton textile were soaked in an aqueous solution of biocide at the concentrations shown, dried, then left in sifted meadow soil containing 25% by weight of water at 25°C for eleven days. With 2-guanidino dodecane phosphate the procedure was modified: the strips were first soaked in a solution of the soluble acetate salt, then in an aqueous solution of trisodium phosphate.

At the end of the test the strips were cleaned, dried, and the tensile strength measured. Results were as follows (mean of ten determinations), textile strength given in lbs.

Preservative	Concentration in solution 1%	0.1%	0.05%
Control	8.8	8.8	8.8
GDA	81.4	76.8	63.3
GDP	87.9*	73.1	69.0
Dodine	64.9	65.0	19.9
Laurylpentachlorophenate	87.0	66.1	55.2

* After 25 days soil burial this figure was 86.7 lbs.

From these data it can be seen that GDP serves to protect cotton textiles and is more effective than the related GDA or dodine.

Example D.

The effect of 2-guanidino dodecane phosphate on the preservation of paper as compared with the acetate salt or with dodine was evaluated by A.S.T.M. test No. 2020.

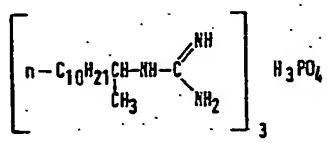
Results, expressed as the % cover of micro-organisms on 2" squares of filter paper after incubation at 25°C were as follows:

Preservative		4 days	20 days
None		70	80
GDA	1%	5	18
	0.1%	7	23
	0.05%	15	40
GDP	1%	1	8
	0.1%	25	77
	0.05%	35	81
Dodine	1%	100	100
	0.1%	100	100
	0.05%	100	100

These results show that the phosphate (applied as in Example C) again is an excellent preservative. However, at low concentrations the preservative activity is lost after 20 days incubation, showing that the material is ultimately biodegradable. Curiously, dodine appeared to supply nutrient to the micro organisms which flourished better in its presence than in the control.

WHAT WE CLAIM IS:—

1. 2-guanidino dodecane phosphate of formula



2. A biocidal composition which comprises as the active ingredient 2-guanidino dodecane phosphate in admixture with at least one diluent or carrier.

3. A composition as claimed in claim 2 which additionally comprises a non-ionic wetting and/or dispersing agent.

4. A composition as claimed in claim 2 or claim 3 wherein the diluent or carrier is a solid inert absorbent carrier.

5. A composition as claimed in claim 4 wherein the carrier is silicaceous earth.

6. A composition as claimed in claim 2 or claim 3 wherein the diluent or carrier is a liquid.

7. A composition as claimed in claim 6 wherein the diluent or carrier is an aromatic hydrocarbon or an alcohol.

8. A composition as claimed in claim 6 or claim 7 which comprises from 0.05 to 5% by weight of 2-guanidino dodecane phosphate.

9. A composition as claimed in claim 8 which comprises from 0.05 to 2% by weight of 2-guanidino dodecane phosphate.

10. A composition as claimed in claim 2 substantially as hereinbefore specifically described.

11. A method of combatting fungal growth which comprises applying to the fungus or to a fungal habitat 2-guanidino phosphate as claimed in claim 1 or a biocidal composition as claimed in any one of claims 2 to 10.

12. A method as claimed in claim 11 wherein the 2-guanidino dodecane phosphate is applied directly to fungus or fungal habitat.

13. A method as claimed in claim 11 wherein the 2-guanidino dodecane phosphate is generated *in situ* by applying to the fungus or fungal habitat a solution of a soluble salt of 2-guanidino dodecane and thereafter adding thereto an aqueous solution of trisodium phosphate.

14. A method of combatting fungal growth as claimed in claim 11 substantially as hereinbefore described with reference to any one of Examples A to D.

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